Prognostic value of troponin T, myoglobin, and CK-MB mass in patients presenting with chest pain without acute myocardial infarction

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Abstract

Objective—To assess the prognostic value of minor myocardial damage in patients presenting with chest pain without myocardial infarction.

Design—The relative risk of suffering a cardiac event in the next six months was assessed in patients with minor myocardial damage assessed by the cardiac markers CK-MB, myoglobin, and troponin T.

Setting—Emergency department of a large university hospital.

Patients—In 128 consecutive patients with chest pain, acute myocardial infarction (by WHO criteria) was ruled out; of these, 39 had a rise and fall of one or more markers, indicating minor myocardial damage. The presence of a documented history of coronary artery disease was assessed on admission.

Results—24 patients had a subsequent event (cardiac death, acute myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting) in the next six months. An abnormal troponin T predicted a subsequent event while abnormal CK-MB or myoglobin did not. The relative risk for troponin T was 2·8 (95% confidence interval: 1·0 to 7·9), for myoglobin 1·0 (0·3 to 3·2), and for CK-MB 0·9 (0·2 to 3·4). A documented history of coronary artery disease predicted subsequent events with a relative risk of 3·9 (1·3 to 11·3).

Conclusions—Troponin T was the only marker that predicted future events, but a documented history of coronary artery disease was the best predictor in patients in whom an acute myocardial infarction had been ruled out.

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The diagnosis of acute myocardial infarction in patients presented to the emergency room with typical chest pain is usually based on the history and on the electrocardiographic (ECG) findings. The detection of myocardial necrosis is then confirmed by the presence of raised serum concentrations of intracellular molecules released into the peripheral blood pool as a consequence of myocardial cell death. The marker most frequently used for this purpose is creatine kinase (CK-MB). A cut-off value for CK-MB is chosen (usually twice the upper limit of normal or on the basis of ROC curves). If the marker rises above this level at the appropriate timepoint with a subsequent fall the diagnosis of acute myocardial infarction is confirmed. Abnormal elevation of biochemical markers or enzymes is one of the three WHO criteria for the diagnosis of acute myocardial infarction.

After an episode of typical chest pain in some patients, however, there is a rise and fall in CK-MB that is above the upper limit of normal but below the predetermined cut-off value. This is usually not diagnosed as acute myocardial infarction but interpreted as indicating severe ischaemia, usually referred to as minor myocardial damage.

Recently, new assays for other markers of myocardial cell necrosis, such as myoglobin and troponin T, have been introduced. The value of these assays in the management of patients with acute myocardial infarction is under investigation.[1] Myoglobin is a very early marker of myocyte damage and may be useful in ruling out an acute myocardial infarction in the first hours after the onset of chest pain.[2] Troponin T may be an even more specific marker for cardiac myocyte damage,[3-7] and some reports show that it is elevated in a substantial proportion of patients with unstable angina, where it suggests a poor prognosis compared to patients with normal values.[8] In patients in whom the CK-MB levels do not rise above the cut-off value—and in whom therefore an acute myocardial infarction can be ruled out—lesser rises in CK-MB reflect minor myocardial damage; in such patients small increases in myoglobin or troponin T may also indicate minor myocardial damage. The prognostic value of these markers, following frequent sampling in the first 24 hours after presentation in the emergency room, has not been studied.

Our aim in this study was to determine the incidence and prognostic significance of minimal elevation of these three markers of myocardial cell damage in patients presenting with chest pain in a hospital emergency room.

Methods

SUBJECTS

Patients with chest pain possibly caused by myocardial infarction and presenting at the cardiac emergency room (a 24 h short stay facility) of the Academic Medical Centre within 12 h of the onset of symptoms were considered for the study. The diagnosis of

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acute myocardial infarction was based on the patient's history and symptoms, abnormalities on a 12-lead electrocardiogram, and a typical rise and fall in the serum CK-MB mass curve with a peak exceeding 15 ng/ml (twice the upper limit of normal). When the diagnosis of acute myocardial infarction was excluded after a period of 24 h they were eligible to participate in the follow up. Exclusion criteria were skeletal muscle damage or trauma, cardiac resuscitation, and inability or refusal to give informed consent. Patients presenting with ST segment elevations on the admission ECG who were treated with thrombolytics and who had no CK-MB elevation ("aborted infarction") were also excluded from the study. A history of coronary artery disease was considered to be present if documented by coronary angiography, a previous myocardial infarction, or a previous positive exercise test.

STUDY PROTOCOL
The study protocol was approved by the ethics committee at our institution. The attending physician noted the time of onset of symptoms (t_0). Blood samples were drawn for measurement of CK-MB, myoglobin, and troponin T at 3, 4, 5, 6, 7, 8, 12, 16, 20, and 24 h after t_0. Only the results of the CK-MB assay at routine time points of 6, 12, 18 and 24 h after t_0 were reported to the attending physician. The results of the other markers under study or at other time points were not known to the physician and all decisions regarding care of the patients were made independently of these measurements.

Patients who were not immediately transferred to the coronary care unit (CCU) because of acute myocardial infarction or severe unstable angina were admitted to the cardiac emergency room waiting for enzyme results and adjustment of medication where appropriate and discharged after 24 h (accelerated angina, Braunwald classification IB).[9] When recurrent symptoms of ischaemia developed or enzyme results indicated myocardial infarction, patients were transferred to the CCU at that point (angina at rest, Braunwald classification IIIB). Patients with severe unstable angina received treatment with aspirin, heparin, and various combinations of β blockers, nitrates, and calcium antagonists. Patients were stabilised and considered for revascularisation only when conservative management failed to control ischaemic episodes. Patients who were discharged after 24 h were also considered for revascularisation during follow up only when medical treatment failed to control their symptoms.

ASSAYS
Blood was collected in 10 ml heparin coated tubes and centrifuged without delay. Cells were discarded and the plasma was stored at −20°C until further analysis.

CK-MB mass assay was performed using the immunochemical method as implemented on the ACS-180 analyser (CIBA Corning), the upper limit of normal being 7·5 ng/ml; there was linearity from 0 to 500 ng/ml.

Myoglobin was measured with a nephelometric assay using the NaLatex myoglobin reagent (Behringwerke) on the Behring Nephelometer 100; range 5–400 ng/ml; upper limit of normal 90 ng/ml.

Troponin T was measured using an ELISA method (Boehringer Mannheim, Germany, product No 1289055) on an ES300 analyser (Boehringer Mannheim); upper limit of normal 0·1 ng/ml; the linearity range of this determination is 0–15 ng/ml.

MINOR MYOCARDIAL DAMAGE
We considered that CK-MB indicated minor myocardial damage if there was a typical rise and fall with a peak above the upper limit of normal (7·5 ng/ml) but less than or equal to twice the upper limit of normal; and that myoglobin indicated minor myocardial damage if the 24 h curve showed a typical rise and fall, with the highest value at least twice the lowest value. Peak myoglobin typically occurred 3 or 4 h earlier then peak CK-MB and occasionally rose above 90 ng/ml.

Troponin T has slow appearance and clearance characteristics and hence a rise and fall cannot be expected within a time window of 24 h; we therefore considered it to be abnormally elevated if there was a gradual rise exceeding a level of 0·1 ng/ml.

FOLLOW UP
All patients were followed up to six months or until an event occurred. We used case note review or telephone interviews to contact the patients, their cardiologist, general practioner, or relatives.

Events were defined as acute myocardial infarction documented by ECG changes and CK-MB elevation, cardiac death, or the need for coronary angioplasty (PTCA) or bypass grafting (CABG) because of the failure of medical treatment to control ischaemic episodes.

STATISTICAL ANALYSIS
The relative risk of suffering a subsequent cardiac event (cardiac death, acute myocardial infarction, CABG, or PTCA) for the 128 patients was calculated with Cox proportional hazards model with CK-MB, myoglobin, troponinT, and a documented history of coronary artery disease as covariates (BMDP Statistical Software). Kaplan-Meier actuarial survival plots were constructed.

Results
During a 16 month period, 309 patients were screened for the study and serum samples were obtained. The diagnosis of acute myocardial infarction was ruled out in 133 patients. For two patients cardiac surgery was already scheduled at the time of presentation and they were also excluded. Therefore 131 patients were eligible for follow up.

Three patients were lost to follow up. Therefore 128 patients formed the study group (98%) and follow up was completed for all patients after six months.

Table 1 Baseline characteristics of the study population

	Total	Markers normal	$\geqslant 1$ Marker elevated
n	128	89	39
Age, years (SD)	63 (13)	62 (13)	66 (12)
Male	78 (61%)	55 (62%)	23 (59%)
Documented CAD	75 (59%)	51 (57%)	24 (62%)
previous AMI	52 (41%)	37 (42%)	15 (39%)
previous CABG	26 (20%)	20 (23%)	6 (15%)
previous PTCA	18 (14%)	12 (14%)	6 (15%)
Medication on admission			
nitrates	46 (36%)	33 (37%)	13 (33%)
β blockers	39 (31%)	25 (28%)	14 (36%)
calcium antagonists	36 (28%)	25 (28%)	11 (28%)
Diagnosis after 24 h			
severe unstable angina (IIIB)	54 (42%)	35 (40%)	19 (49%)
accelerated angina (IB)	59 (46%)	43 (48%)	16 (41%)
arrhythmia	2 (1·6%)	2 (2%)	0
atypical chest pain	13 (10%)	9 (10%)	4 (10%)

CAD, coronary artery disease; AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; PTCA, percutaneous transluminal coronary angioplasty; IIB, IB, Braunwald classification of unstable angina IIIB, IB.
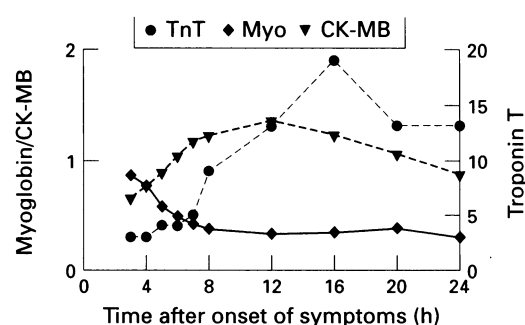
Figure 1 Marker pattern indicating minimal myocardial damage. Typical release pattern of markers showing minimal myocardial damage in the first 24 h after the onset of symptoms. Markers are expressed as multiples of the upper limit of normal. Myo, myoglobin; TnT, troponin T.

The baseline characteristics of the study population are given in table 1. We obtained CK-MB results indicating minor myocardial damage in 13 patients, myoglobin results in 20, and troponin T results in 24. In some patients more than one marker was raised so there were 39 out of 128 patients (30%) with one or more markers suggestive of minor myocardial damage. None of the baseline characteristics was different between the group with all markers normal and the group with one or more markers abnormal. Fifty four patients were classified as having severe unsta-

Table 2 Events during 6 months follow up

Case	Age (years)	Documented CAD	CK-MB	TnT	Myoglobin	Event	Event-free (days)
1	57	+(a/c/p)	0	0	+	PTCA	137
2	66	+(c)	0	+	0	PTCA	3
3F	68	+(a/c/p)	0	0	0	PTCA	58
4F	79	+	0	0	0	PTCA	4
5F	86	+	+	+	+	Infarct	4
6	41	+(a/p)	0	0	0	PTCA	3
7	65	0	0	0	0	Infarct	41
8	75	0	0	0	0	Bypass	19
9F	82	+	+	+	+	PTCA	39
10F	77	+(a)	0	0	0	PTCA	48
11	43	0	0	0	0	PTCA	1
12F	57	+(a)	0	0	0	PTCA	1
13F	81	+	0	+	+	Bypass	11
14	74	+	0	0	0	PTCA	122
15	59	+(a/c)	0	0	0	Death	167
16	57	+(a/c)	0	0	0	PTCA	14
17F	67	+(p)	+	+	+	PTCA	1
18F	68	+(a/p)	0	0	0	PTCA	1
19	67	+(a/c)	0	+	0	PTCA	3
20	68	+(a/c/p)	0	0	0	PTCA	3
21F	81	+	0	0	0	Bypass	133
22F	75	+(a)	0	0	0	PTCA	1
23	46	+	+	+	0	PTCA	3
24	50	0	0	+	0	PTCA	4

CAD, coronary artery disease; TnT, troponin T; a, acute myocardial infarction; c, CABG; p, PTCA; F, female; +, present; 0, absent.
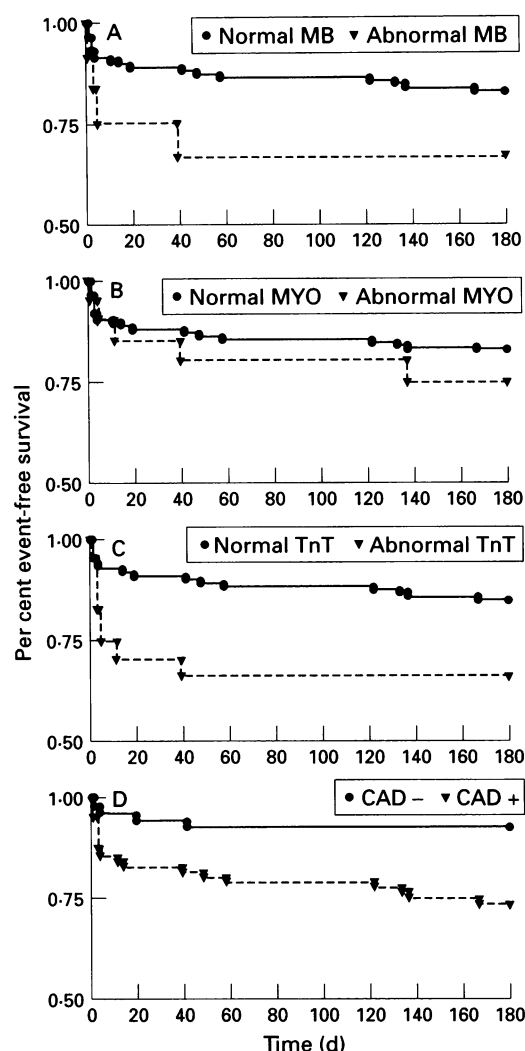The patient who suffered a non-cardiac death is not listed in this table.

Table 3 Frequency of cardiac events and relative risks (RR) of an event for abnormal marker levels and history of coronary artery disease (CAD).

	Result	Event/number	RR	95% confidence limits
Troponin T	+	8/24 = 33%	2·8	1·0 < RR < 7·9
	0	16/104 = 15%		
Myoglobin	+	5/20 = 25%	1·0	0·3 < RR < 3·2
	0	19/108 = 18%		
CK-MB	+	4/13 = 31%	0·9	0·2 < RR < 3·4
	0	20/115 = 17%		
Documented CAD	+	20/75 = 27%	3·9	1·3 < RR < 11·3
	0	4/53 = 8%		

Results of multivariate Cox proportional hazards analysis. RR, relative risk; +, abnormal level of marker concentration/documented CAD; 0, normal level of marker concentration/no documented CAD.

ble angina (IIIB) and admitted to the CCU and stabilised. Fifty nine patients were classified as having accelerated angina (IB) and after adjustment of medication these patients were discharged after 24 h. Thirteen patients were eventually classified as having atypical chest pain.

Figure 1 shows a typical pattern of marker release in the first 24 h after the onset of symptoms. The markers are expressed as multiples of the upper limit of normal. The CK-MB rises to a peak of 11·5 ng/ml at t_8 and this patient is therefore classified as not having acute myocardial infarction. The pattern of the markers, however, strongly suggest that some release of markers from the myocardium has taken place and this is therefore termed minor myocardial damage. This patient did not suffer an event during the follow up period. Table 2 shows the 24 patients who experienced an event during the follow up period of six months. There were two deaths, one cardiac death after 167 days, and one non-cardiac death after 18 days. Two patients suffered a myocardial infarct, one after four days (patient 5, who had all three markers abnormal) and one after 41 days (patient 7, who had no abnormal markers). Three patients underwent CABG after 11, 19, and 133 days respectively. Eighteen angioplasty procedures were performed, of which 13 were within the first week of hospital admission. Table 3 shows the incidence of cardiac events and the multivariate analysis of relative risk of an event for the three markers and for the presence of coronary artery disease. Abnormal troponin T has a relative risk of 2·8 and was the only marker that was a significant independent predictor for future events in this analysis. Abnormal myoglobin has a relative risk of 1·0. Note that a documented history of coronary artery disease has a relative risk of suffering an event of 3·9.

Figure 2 shows the Kaplan-Meier survival curves, giving the difference in event-free survival for the patients with minor myocardial damage, as indicated by the three marker, versus the patients without myocardial damage. A documented history of coronary artery disease was also shown to be a significant clinical predictor for future events in this analysis. One patient was removed from the analysis after 18 days when she died after a traumatic hip frac-

Figure 2 Kaplan-Meier survival curves. The event-free survival of patient groups with minimal myocardial damage as indicated by one of the three markers or by documented coronary artery disease using Cox proportional hazard model with the three markers and documented history as covariates. MMD, minor myocardial damage; MYO, myoglobin; MB, CK-MB; TnT, troponin T; CAD+, documented history of coronary artery disease; CAD−, no documented history of coronary artery disease.

Figure 3 Cumulative proportion of abnormal troponin T. Cumulative proportion of troponin T results above 0·1 ng/ml in the group of 24 patients with an abnormal troponin T plotted against the time from onset of symptoms.

ture (non-cardiac death). All other patients were at risk for an event for the full period of 180 days or until an event occurred.

Figure 3 shows the cumulative proportion of troponin T samples that were above 0·1 ng/ml for each time point after the onset of symptoms in the group of 24 patients with abnormal troponin T results. This proportion reached 100% 16 h after the onset of symptoms.

Discussion

In the emergency room where patients with chest pain are triaged for admission to the CCU, sensitive markers for cardiac damage are of great importance. Minor elevation of CK-MB without concomittant elevation of

total serum CK may indicate ischaemia or infarction and probably has a good prognosis.[1][10-12] CK-MB mass,[1][13][14] myoglobin,[15-18] and troponin T[6][19] are very sensitive markers for myocardial damage. The use of markers of increased sensitivity and very frequent sampling, however, may result in a diagnosis of myocardial infarction being made more often. In our study repeated measurement of markers for myocardial infarction suggested that the results cannot be interpreted only as either "normal" or "definite acute myocardial infarction". There is an intermediate release pattern suggesting minor myocardial muscle damage but not fulfilling the criteria for acute myocardial infarction. It is important to know if this pattern identifies a group of patients at high risk for subsequent events. Minor myocardial damage may be caused by episodes of transmural ischaemia and very early spontaneous reperfusion leading to a small area of subendocardial necrosis, with a larger area at risk for subsequent infarction. Thus minor myocardial damage could be a sign of a larger area in jeopardy. However, some evidence suggests that enzyme release from cardiac myocytes can take place without irreversible cell damage[20][21] and minor myocardial damage would then reflect severe ischaemia.

Troponin T was reported by Hamm et al to be raised in a substantial percentage of patients with unstable angina and normal CK-MB levels, and was related to poor prognosis.[8] That study was done in patients with severe unstable angina and the cut-off level for troponin T was set at 0·2 ng/ml. Blood was collected every eight hours, so minor short lasting CK-MB elevations could have been missed. A high death rate within the first week may indicate a high prevalence of cardiogenic shock or respiratory failure that is associated both with minor marker elevation and poor prognosis.[10]

Figure 1 shows a typical marker release pattern: a CK-MB curve with a rise and fall but with a peak not exceeding 15 ng/ml. The peak value occurs between eight and 16 hours after the onset of chest pain. Myoglobin shows an initial value of 82 ng/ml and quickly declines. The time window in which the marker is raised starts very early after the onset of symptoms and is much narrower than for CK-MB. Troponin T has slower release and elimination kinetics and remains raised for a longer period of time. This may explain why in unstable angina with several episodes of ischaemia and an uncertain time of onset of symptoms troponin T is raised more often than CK-MB, depending on the timing and frequency of sampling.

The demonstration of minor myocardial damage, in contrast to acute myocardial infarction or "normal", highlights the problem of the meaning of the diagnosis "acute myocardial infarction". The widely used WHO criteria require the fulfilment of two of three criteria: a clinical one (typical chest pain of more than 20 minutes duration suggestive of acute ischaemia), an electrocardiographic one (ST segment elevation or new pathological Q waves), and a biochemical one (typical
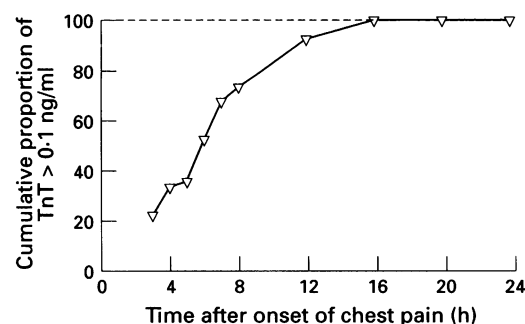
rise and fall with the peak value exceeding a certain reference value). In the presence of acute thrombotic occlusion of a large epicardial coronary artery, these criteria will be met unequivocally. However, in the event of occlusion of smaller coronary branches, extensive collateral circulation to the ischaemic area, or prolonged ischaemia due to other causes (arrhythmias, shock, blood pressure changes in patients with left ventricular hypertrophy), the classical clinical or electrocardiographic findings may not be present and much more depends on the strictness of the definition of abnormal elevation of the biochemical markers. The definition of "abnormal" is then a trade-off between sensitivity and specificity on the one hand and the clinical relevance of the resulting classification on the other.

Studying prognosis highlights the clinical relevance of minor myocardial damage in the setting of the emergency room. With this approach we showed that where the diagnosis of acute myocardial infarction was excluded on the basis of CK-MB measurements, minor myocardial damage can be detected with frequent measurement of CK-MB, myoglobin, and troponin T in a substantial proportion of patients. We considered minor myocardial damage to be present on the basis of 10 blood samples taken at frequent intervals in the first 24 hours after the onset of symptoms. However, we could not show that the identification of minor myocardial damage by the CK-MB or myoglobin results provided useful prognostic information in this patient group. Figure 3 gives the cumulative proportion of troponin T samples above 0·1 ng/ml in the group of 24 patients with abnormal troponin T values. It shows that in this group of patients it took 16 hours before all 24 patients had values above 0·1 ng/ml. This suggests that admission samples (usually taken two to six hours after the onset of symptoms) will probably underestimate the proportion of troponin T positive patients.

The attending physician was blinded to the troponin T and myoglobin results, but of course was aware of the patient's history of coronary artery disease. The patient's documented history is usually readily available on admission. Most "events" were revascularisation procedures, and the physician who decided to perform the revascularisation was aware of the patient's history of coronary artery disease. This may have caused a bias towards more events in this group. However, patients were treated according to a conservative management strategy and were considered for revascularisation only if this failed to control their symptoms. Therefore comparison of the relative risk of a history of coronary artery disease and minor myocardial damage as indicated by the three markers seems justified. In the multivariate analysis, abnormal troponin T bore a relative risk of 2·8, independent of the other variables. The troponin T results provide important prognostic information over and above that provided by a documented history of coronary artery disease. Whether a different approach towards patients with unstable angina with elevated troponin T improves prognosis remains to be determined.

We conclude that frequent sampling of CK-MB, troponin T and myoglobin identifies minor myocardial damage in a substantial number of patients in whom an acute myocardial infarct has been ruled out. A history of coronary artery disease is the best predictor of future cardiac events in these patients. Of the three markers tested in this study only an abnormal troponin T can be identified as an independent additional risk factor.

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